PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS: HISTORICAL EXAMPLES AND SHELF-LIFE EXTRAPOLATION

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ABSTRACT

Amorphous solid dispersions (ASDs) of a poorly water-soluble active pharmaceutical ingredient (API) in a polymer matrix can enhance the water solubility and improve the bioavailability of the API. Many ASD products are kinetically stabilized, and the inhibition of crystallization of an API within and beyond shelf life is still a matter of debate, since the formation of crystals may impact bioavailability. We present the first literature examples of ASD long-term stability studies over up to 25 years under ambient storage conditions where no API crystallization was observed. Additionally, a risk assessment and mitigation strategy of API crystallization in packaged ASD drug products (DP) is outlined. The risk of shelf-life crystallization and the respective mitigation steps are assigned for different DP development scenarios. Ultimately, the physical stability of ASD DPs during shelf-life storage is modeled by quantifying crystal growth kinetics by transmission Raman spectroscopy (TRS), modeling the impact of water sorption on the glass-transition temperature of the ASD, and predicting the moisture uptake by the packaged ASD DP during storage. This approach is applied to an ASD of an AbbVie-internal compound showing stability beyond the anticipated shelf-life.

Keywords: Amorphous Solid Dispersions, Crystal Growth, Transmission Raman Spectroscopy, Shelf-Life, Risk-Assessment

INTRODUCTION

Poor aqueous solubility and therefore scarcity of bioavailability of active pharmaceutical ingredients (APIs) is one of the main challenges in the development of solid oral dosage forms during the last few decades in the pharmaceutical industry.[1, 2] Formulating the API as an amorphous solid dispersion (ASD) has been proven to successfully enhance bioavailability of many APIs classified as biopharmaceutical classification system (BCS) class II and class IV.[3, 4] Many ASD formulations are thermodynamically unstable but kinetically stabilized due to low molecular mobility in the glassy ASD formulation.[5, 6] Accelerated API crystallization at high drug loads (DL) in kinetically stabilized ASDs is considered a potential risk for both, patients and pharmaceutical companies.[7]

In this work the long-term physical stability of two kinetically stabilized ASDs is presented: a 15 %DL ASD of Fenofibrate was investigated after 15 years of storage under uncontrolled ambient conditions, and a 20 %DL ASD of Nifedipine even after 25 years.[8, 9] Those observations show that even kinetically stabilized ASDs can be crystal free way beyond the desired pharmaceutical shelf-life.

Additionally, a strategy for crystallization risk assessment of ASD products, based on monitoring crystal growth in ASDs using transmission Raman spectroscopy (TRS), is discussed. Our approach classifies the crystallization risk in the drug product (DP) based on accelerated open dish studies. Depending on the observed data, proper mitigation steps are advised. In case of an anticipated crystallization in the packaged DP over shelf-life, the actual crystal growth in the DP is estimated. For this step, open dish crystallization rates obtained at accelerated conditions are combined with modeling of the glass transition temperature T_g and water content of the packaged DP during storage.

RESEARCH CONCEPT

One of the key factors in ASD formulations is the optimization of the drug load. It is essential that the drug

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load of an oral dosage form is as high as possible from a commercial point of view because smaller dosage forms and lower pill burden are typically better tolerated.[10] A higher drug load in turn often reduces the physical stability of the ASD formulation in terms of API crystallization.[11] From a thermodynamic perspective, the API is dissolved in an amorphous polymeric matrix. However, in many ASD formulations, the API content exceeds its solubility in the matrix at storage conditions: the ASD is thermodynamically unstable but kinetically stabilized due to low molecular mobility in the glassy ASD.[5, 6] In general, by increasing the drug load in kinetically stabilized ASDs, the degree of supersaturation of the dissolved API in the matrix and, therefore, the thermodynamic driving force for API crystallization is increased.[12] In addition, many APIs have a lower glass-transition temperature (T_g) than the polymer, leading to reduced T_g of the ASD with increasing drug load (**Figure *1***).[8, 13] Such a decrease of T_g increases the molecular mobility and therefore reduces kinetic stabilization of the ASD.[14, 15]

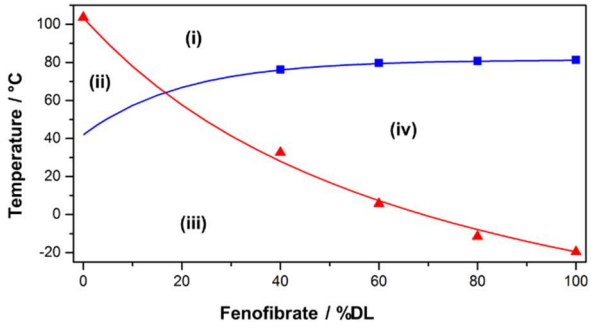

Figure 1: Exemplary phase diagram of a polymer-fenofibrate system.[9] The solubility temperature at different compositions is depicted in blue. The measured T_g values of different compositions are depicted in red. The symbols reflect measured data and the curves show modeling results. Different regions can be identified in the phase diagram: (i) thermodynamically stable melt, (ii) thermodynamically stable glass, (iii) kinetically stable glass and (iv) the undercooled or unstable melt, respectively.

The extend of stabilization and the required difference between storage temperature T and T_g of ASDs for avoiding API crystallization have been a matter of discussion in the literature for decades. As a rule of thumb, it has been assumed that a kinetically stabilized ASD needs to be stored at least 50 °C below T_g.[16] Assuming such an unnecessary high safety margin will hinder the development of high-drug load ASDs with low T_g. However, setting the safety margin to low will cause a potential patient safety risk. As a first measure to determine the physical stability of kinetically stabilized ASDs, long term stability studies have been conducted. In our studies we could show that no crystallization of the drug active is observed in ASDs of Nifedipine and Fenofibrate stored only 30 °C and even 8 °C below T_g after 15 years and 25 years of storage, respectively.[8, 9]

Despite those examples of long-term stability of kinetically stabilized ASDs, the demand for higher drug load and the occurrence of API crystallization in developmental stability studies makes it necessary for pharmaceutical development teams to have a proper risk assessment and mitigation strategy at hand. As time is of the essence in pharmaceutical development, we have developed a lean approach for API crystallization risk assessment in ASDs based on fast open dish studies, which excludes the patient risk of API crystallization over shelf-life storage while properly balancing the business risks involved (**Figure *2***).[17]

The starting point of the risk assessment is the standard open dish stress test at 40 °C / 75% RH. Ifcrystallization is detected in this study within 14 days of storage, an investigation of the crystallization risk is indicated. As in this stage of development crystallization is usually detected qualitatively by polarized light microscopy, the next step is to quantify the crystal growth and assign a rate constant. This investigation is performed in a Tier I investigation, preferably using TRS. In our experience, the non-destructive nature, inherent sample averaging, and chemometric data evaluation make this technology more than suited to quantify crystal growth in ASD samples. From our work on long term stability, we can assume that an ASD taking 14 days or longer to show complete API crystallization in an open dish experiment at 40 °C / 75% RH will not present a crystallization risk during shelf-life storage of the packaged material.[9] In cases where the ASD under investigation shows a considerable crystallization rate, the physical stability of alternate formulations can be compared in a Tier II study. A Tier III investigation is indicated if no alternate formulation with sufficient stability is found, or other reasons, like bioavailability or manufacturability, indicate the usage of a formulation considered not physically stable. In the Tier III investigation, the crystallization rate constant is measured for several storage conditions above T_g. The rate constants can be correlated with the ratio of T_g over T. Calculations of the moisture dependence of the T_g in the ASD and moisture content of the packaged DP can be used to determine the T_g of the product during storage.

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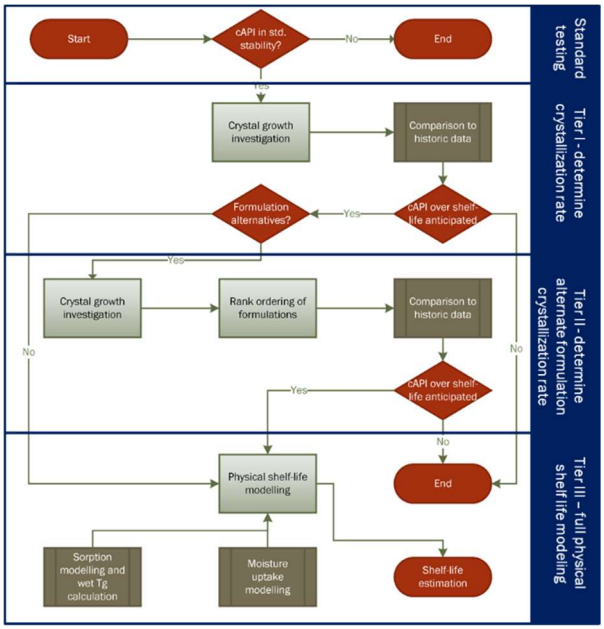

Figure 2: Workflow of the physical shelf life modelling risk assessment strategy for crystallization in ASD formulations. An investigation of the physical stability is indicated if API crystallization is observed in the standard open dish stability investigation at 40 °C / 75% RH within two weeks. In a Tier I investigation, the rate of crystallization in the ASD is determined. If crystallization is sufficiently fast to indicate a shelf life risk, the crystal growth rate in alternate formulations is determined in a Tier II investigation. If no sufficiently stable formulation can be used, a Tier III investigation is indicated and the crystal growth of the DP in the primary packaging container is approximated.

RESULTS

The risk assessment strategy is now routinely applied to AbbVies ASD development candidates. The application of the complete risk assessment strategy on a model compound will be presented in this talk. After crystallization of the lead formulation candidate was observed in an open dish study, the rate of crystallization was determined and compared to alternate formulations (**Figure *3***). As the lead formulation had shown complete API crystallization within 3 days at 40 °C / 75% RH open dish condition, an estimation of the physical shelf-life was indicated. Based on predicted water content of the blister packaged DP and calculated impact of water on the products T_g, a shelf-life till crystallinity limit of 67 months could be estimated.

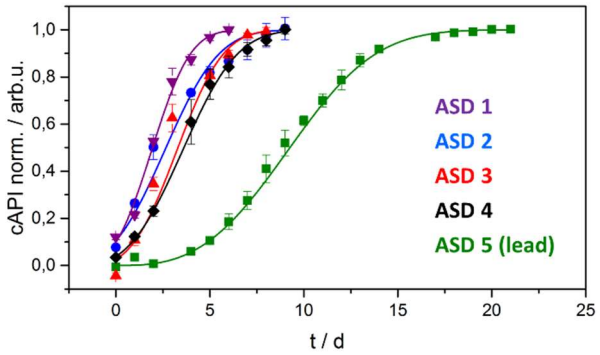

Figure 3: Crystal growth in five different ASD formulation candidates of an AbbVie internal compound. The crystal growth was recorded in samples stored at 30 °C / 75 %RH (open dish) using TRS. The fraction of crystallized API normalized to total API is shown in dependence of time.

DISCUSSION

Our investigations of nifedipine and fenofibrate ASD DPs present, up to now, the only long-term stability investigations of kinetically stabilized ASDs in the literature and proved that such DPs can be safe over the shelf-life, even if stored only a few degrees below T_g. As crystallization still might occur in accelerated stability studies, pharmaceutical development teams require a strategy to assess and mitigate crystallization risk. An essential step in developing the presented fast risk assessment approach was determining the relation of the API crystallization rate with the environmental conditions. In the literature, different attempts can be found from simple Arrhenius extrapolation approaches to linking the crystallization with relaxation time in glasses. Utilizing recent glass physics approaches, we could successfully correlate the logarithm of the crystallization rate with the ratio of T_g over T. Combining this approach with the modeling of the water uptake of the packaged DP and the water induced change in T_g, we were able to estimate crystal growth in packaged DP based on fast open dish studies. Applying the risk assessment and mitigation strategy as presented in **Figure *2*** is aiding project development teams in making proper decisions regarding the crystallization risk of the ASD DP. In cases where crystallization of the API over the shelf-life is anticipated, a safe shelf-life range or an alternate packaging material can be suggested.

CONCLUSIONS

With the results presented in this work, crystallization observed in open-dish studies is no longer a

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showstopper in ASD development. Using historical examples, the possibility of long-term stability in kinetically stabilized ASDs even if stored only a few degrees below T_g could be shown. Utilizing recent results of the investigation of glass physics in ASDs and combining them with physical modeling tools, a risk assessment and mitigation framework for API crystallization in ASD formulation could be developed. The framework enables drug development teams to conduct rational risk-based actions in ASD development. It allows to successfully bring ASD formulations to market that were just a couple of years ago discontinued due to perceived stability issues.

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REFERENCES

1. Thayer, A.M., *FINDING SOLUTIONS.* Chemical & Engineering News Archive, 2010. **88**(22): p. 13-18.
2. Waring, M.J., et al., *An analysis of the attrition of drug candidates from four major pharmaceutical companies.* Nature Reviews Drug Discovery, 2015. **14**(7): p. 475-486.
3. Schittny, A., J. Huwyler, and M. Puchkov, *Mechanisms of increased bioavailability through amorphous solid dispersions: a review.* Drug Delivery, 2020. **27**(1): p. 110-127.
4. Pandi, P., et al., *Amorphous solid dispersions: An update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products.* International Journal of Pharmaceutics, 2020. **586**: p. 119560.
5. Lehmkemper, K., et al., *Long-Term Physical Stability of PVP- and PVPVA-Amorphous Solid Dispersions.* Mol Pharm, 2017. **14**(1): p. 157-171.
6. Zhou, D., et al., *Assessing Physical Stability Risk Using the Amorphous Classification System (ACS) Based on Simple Thermal Analysis.* Molecular Pharmaceutics, 2019. **16**(6): p. 2742-2754.
7. Yu, L., *Amorphous pharmaceutical solids: preparation, characterization and stabilization.* Advanced Drug Delivery Reviews, 2001. **48**(1): p. 27-42.
8. Theil, F., et al., *Frozen in Time: Kinetically Stabilized Amorphous Solid Dispersions of Nifedipine Stable after a Quarter Century of Storage.* Mol Pharm, 2017. **14**(1): p. 183-192.
9. Theil, F., et al., *Extraordinary Long-Term-Stability in Kinetically Stabilized Amorphous Solid Dispersions of Fenofibrate.* Molecular Pharmaceutics, 2017. **14**(12): p. 4636-4647.
10. Mudie, D.M., et al., *A novel architecture for achieving high drug loading in amorphous spray dried dispersion tablets.* International Journal of Pharmaceutics: X, 2020. **2**: p. 100042.
11. Gupta, P., V.K. Kakumanu, and A.K. Bansal, *Stability and Solubility of Celecoxib-PVP Amorphous Dispersions: A Molecular Perspective.* Pharmaceutical Research, 2004. **21**(10): p. 1762-1769.
12. Zhou, D., et al., *Thermodynamics, molecular mobility and crystallization kinetics of amorphous griseofulvin.* Mol Pharm, 2008. **5**(6): p. 927-36.
13. Amharar, Y., et al., *Solubility of crystalline organic compounds in high and low molecular weight amorphous matrices above and below the glass transition by zero enthalpy extrapolation.* Int J Pharm, 2014. **472**(1-2): p. 241-7.
14. Kothari, K., V. Ragoonanan, and R. Suryanarayanan, *Influence of molecular mobility on the physical stability of amorphous pharmaceuticals in the supercooled and glassy States.* Mol Pharm, 2014. **11**(9): p. 3048-55.
15. Hancock, B.C., S.L. Shamblin, and G. Zografi, *Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures.* Pharm Res, 1995. **12**(6): p. 799-806.
16. Amidon, G.L., et al., *A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability.* Pharm Res, 1995. **12**(3): p. 413-20.
17. Liu, B., et al., *Crystallization Risk Assessment of Amorphous Solid Dispersions by Physical Shelf-Life Modeling: A Practical Approach.* Mol Pharm, 2021. **18**(6): p. 2428-2437.

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